citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.

10. (Amended) A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to produce and to maintain, for at least 2 hours in 0.075M sodium chloride, a concentration of dissolved sertraline which is at least 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.

15. (Amended) A composition of matter comprising sertraline or a pharmaceutically acceptable salt thereof and an amount of a solubilizing agent sufficient to effect, *in vivo,* a C_{max} and/or an AUC which is greater by at least 10% than the C_{max} and/or AUC effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.

22. (Amended) A method of increasing the solubility of sertraline in an aqueous chloride ion-containing use environment, comprising administering said sertraline to said use environment in a composition of matter additionally comprising a solubilizing agent, provided said solubilizing agent is not alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.

REMARKS/ARGUMENTS

Claims 1 through 29 remain in this application. The claims presented are those which were (once) amended during the international (PCT) phase.

Claims 1, 10, 15, and 22, the independent claims in the instant application, have each been amended in parallel to exclude certain substances (sesame oil, peanut oil, sodium lauryl sulfate) which are disclosed in the prior art and which would or might be useful in Applicants' invention. The significance of these amendments in advancing the prosecution of this application is discussed below. It is noted that the remaining substances excluded by proviso from claims 1, 10, 15, and 22 (alginic acid, sodium citrate, calcium carbonate, polyethylene glycol having a molecular weight greater than 3350) were excluded during international prosecution.

As a preliminary comment, it is noted the invention was made in response to a phenomenon, newly discovered, that is problematic specifically in respect of sertraline. That is, sertraline salts exhibit a tendency to form a gel and/or exhibit reduced solubility when exposed to a use environment containing chloride ions (e.g., the gastrointestinal tract). The phenomenon appears to become more problematic as the solubility of the particular salt increases. This phenomenon can create therapeutic difficulties by unexpectedly altering the release profile of a dosage form.

Claims 1-29 stand rejected under 35 USC 103(a) as being unpatentable over EP 0 415 612 or Ranade 4,803,076 or Bacopoulos each taken alone or in view of Thakkar et al. 4,847,092. The Examiner appeared to take the position that at least some of the substances claimed by Applicants for use as solubilizers with sertraline are commonly known for use as excipients with other compounds, and that it would therefore be obvious to use them in conjunction with sertraline.

As a preliminary consideration, it is believed that Bacopoulos and EP 0 415 612 are members of the same patent family and that, as such, neither adds anything not already disclosed by the other, i.e., the specifications of the two documents appear to be the same. Thus these two references are collectively referred to as a single reference, "Bacopoulos", in the discussion which follows.

As a further preliminary consideration, the Examiner is respectfully urged to reconsider his position, particularly in light of the instant amendments, on the basis that Applicants have discovered the solution to a problem, the problem being gelation/decreased solubility of sertraline in a chloride-containing

environment, and that that solution is embodied in the claims. The solution to a problem cannot be obvious if the existence of the problem itself was not appreciated prior to the invention, as in the instant case. Thus any impact by the prior art with respect to the instant claims was, at best, accidental, and has been cured by the instant amendments.

Further, without some motivation provided by the prior art to use the solubilizer substances embodied in the claims in sertraline-containing formulations, the invention cannot be obvious. It is respectfully submitted that the fact that such substances are known or could be used as excipients does not provide the requisite motivation. The only way one skilled in the art would find Applicants' invention obvious is through the use of hindsight, which is well known not to be the standard for patentability. The law is in fact emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

The documents (Ranade and Bacopoulos) cited by the Examiner have been carefully reviewed With respect to Ranade, the Examiner seems to be reasoning that a lubricant (which functions as a tabletting aid) such as the magnesium stearate disclosed in Ranade's Example 4 and, by incorporation, Example 5, is an organic acid salt, or that it fits within another of the categories of solubilizers disclosed by Applicant. Applicant traverses this reasoning on the basis that such lubricants are poorly soluble in water, and would accordingly be unable to influence the solubility of sertraline without themselves being soluble, and that they are thus outside the scope of Applicant's claims. In different words, magnesium stearate

would not be able to produce a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of the magnesium stearate. Magnesium stearate is, accordingly, outside the scope of Applicants' claims.

Bacopoulos incidentally disclosed a composition which can contain certain excipients that are useful in Applicant's invention. Such excipients have now been removed from the claims by proviso. The claims now specify that a composition according to the invention does not include alginic acid, sodium citrate, calcium carbonate, sesame oil, peanut oil, sodium lauryl sulfate or a polyethylene glycol having a molecular weight greater than 3350.

Considering that the amendments to Applicant's claims remove any incidental overlap between Bacopoulos and the instant application, Bacopoulos will be seen not to affect the patentability of the invention defined by Applicant's claims since it mentions nothing relating to the problem Applicant has solved, i.e., solubilization, and is not even remotely suggestive of that problem.

Thakkar adds nothing to the disclosures of Ranade and Bacopoulos that would affect patentability. Thakkar relates to an orally administerable sustained release pharmaceutical formulation which is a hydrophobic carrier matrix in which diffusion channels are created so as to facilitate the entry of water into the formulation to dissolve the pharmaceutically active agent and permit its release over a prolonged period of time (column 2, lines 34-40). Thakkar incidentally discloses that glycerides and partial glycerides may be used as the hydrophobic carrier. But Thakkar discloses nothing relating to solubilizing any of the compounds he mentions; Nor is sertraline, the active principle to which Applicants' invention is directed, mentioned. It is submitted that Thakkar can have no effect on obviousness if Thakkar mentions neither the active agent to which the instant claims are directed nor the problem which Applicants have solved. It may be coincidental that Thakkar mentions a few excipients which are useful as solubilizers in Applicants' invention, but it cannot be obvious to use them as such if Thakkar says nothing about any solubility problem or provides any other motivation.

It is accordingly respectfully submitted that any incidental overlap between Applicants and the primary references has been eliminated. It would not be obvious to use any of the other substances covered by Applicants' claims in a sertraline-containing formulation because none of the references addresses the solubilization problem that Applicants' invention solves.

It is accordingly respectfully requested that the rejection over Ranade and Bacopoulos and Thakkar be withdrawn.

Claims 1-29 stand rejected under 35 USC 112, the Examiner having taken the position that the instant claims are not defined by ranges of amounts of the critical components which are disclosed as necessary to achieve the improved solubilization effect of sertraline in chloride ion containing solution. The rejection is traversed on the basis that amounts are indeed included in all of the claims, albeit in functional language. The undersigned knows of no reason prohibiting the use of functional language in the claims, however.

Each of independent claims 1, 10, 15, and 22 contains the requirement that, in a sertraline composition containing a solubilizer, the solubilizer be present in an amount "...sufficient to produce a concentration of dissolved sertraline in a use environment containing chloride ions which is 1.5 times higher than the concentration effected by a comparative composition of matter identical thereto but for the inclusion of said solubilizing agent..." This language was in fact employed because it (1) ensured that the improved solubility would be due to the solubility agent and (2) is definite in apprising those skilled in the art of exactly the amount of a given solubilizing agent, i.e., an amount sufficient to produce a concentration of dissolved sertraline that is higher by a factor of 1.5 relative to not including that solubilizing agent. It is submitted that this language is clear to one skilled in the art, particularly in light of the specification which contains extensive explanation about, and description of, the invention, including tests which can be conducted *in vivo* and *in vitro*. See, for example, pages 3-5 of the specification.

The claims stand rejected under 35 USC 112 for additional reasons, all of which are discussed following:

The Examiner objected to the term "comparative". The rejection is traversed on the basis that terms in claims are interpreted in light of the

specification, and that the term is abundantly defined in the specification, for example at page 2, lines 21 to 24, and at page 24, lines 8-10. One skilled in the art would clearly understand Applicants' meaning, i.e., that a comparative composition is a composition identical to the solubilized composition except for the solubilizer, i.e., the comparative composition doesn't contain one.

Likewise, the terms "immediate release dosage form" and "controlled release dosage form" are terms abundantly well known to those skilled in the art, plus the fact that these terms are well explained in the specification. See page 7, lines 14 to 24.

The Examiner additionally took the position that the invention is limited to "tablets", rather than the broader "composition of matter" terminology employed in the claims. The rejection is traversed on the basis that Applicants made it abundantly clear that (1) their compositions are suitable for formulating into all types of oral dosage forms including tablets, capsules, multiparticulates, powders for oral suspension, and unit dose packets (sometimes referred to in the art as a "sachet"); (2) their compositions can be used in liquid dosage forms such as oral solutions or suspensions and injectable formulations; and (3) that, for making the compositions of the invention into oral dosage forms, conventional techniques known to the art can be employed. See page 2, lines 27 et seq. It is respectfully submitted that this ground of rejection be withdrawn.

The Examiner additionally contended that Applicants' claimed composition of matter is not described in terms which indicate the utility of same to treat a condition or disease. The rejection is traversed on the basis that the invention relates to sertraline, a known compound whose utilities are also well known. Applicants' disclose known sertraline utilities including, for example, use as an antidepressant and anorectic agent, and in the treatment of obsessive-compulsive disorder, premenstrual dysphoric disorder, post-traumatic stress disorder, chemical dependencies, anxiety-related disorders, panic and premature ejaculation. See Applicants' specification.at page 1, lines 11-14.

The Examiner additionally contended that the term "solubilizing agent" does not define chemical compounds, such as those of claim 7, which are described as useful. The rejection is traversed on the basis that one skilled in the art would

readily understand exactly the types of compounds to which Applicants refer based on the examples given, i.e., the organic acids disclosed at page 8, lines 7-15 and the other categories exemplified in Tables 1 and 2. There is no term mentioned in claim 7 which is not exemplified and/or otherwise clarified in the specification.

The Examiner additionally contended that the method of claim 23 is not limited to "solubilizing agents" capable of yielding compositions having the effective comparative properties. The rejection is traversed and/or not understood, It being submitted that the claim language is parallel to other claims and that it is abundantly clear. The claim clearly requires that the sertraline concentration provided by a sertraline composition also containing a solubilizing agent be increased by a factor of 1.5 relative to the sertraline concentration provided by a comparative composition not containing the solubilizing agent. The language is clear in describing the requirements of a solubilizing agent in terms of a control (i.e., comparative) composition. One skilled in the art is familiar with the language and concepts presented (i.e., the concept of a control composition) and would find the language to be clear and distinct.

Claims 1-27 stand rejected under obviousness-type double patenting over copending Serial Nos. 09/380977, 09/380825, and 09/380900. It is believed that "09/380977" is a misprint for "09/380897". Also, it is believed the Examiner also meant to base the rejection on 09/380,885 rather than 09/380,825, since the latter Serial Number belongs to the instant application.

The rejection is traversed on the basis that neither 09/380,897 nor 09/380,885 contains claims that relate to solubilizing agents or to solubilization at all. It is not seen that the claims of either application discloses substances that are also disclosed in the claims as being solubilizing agents. Thus it is not seen how the claims of the instant application which are directed to solubilized sertraline compositions and methods could be obvious from the claims of the aforementioned two double patenting references which disclose nothing about solubilizing anything. It is accordingly respectfully requested that the double patenting rejection be withdrawn with respect to these two references.

09/380900 discloses gelatin-encapsulated solution dosage forms of sertraline. The claims say nothing relating to solubilization or improving the